REMARKS

Applicants have amended the title to more specifically describe the invention and the specification to correct inadvertent typographical errors in the references to SEQ ID NOs and mis-numbering of the tables. Applicants maintain that the amendments add no new matter.

Applicants have cancelled Claims 30, 31, and 36, without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended the claims to remove reference to the Figures. Claims 22-27 and 35 have been amended to remove reference to the extracellular domain. Claims 22-26 and 35 have been amended to add the limitation that the claimed nucleic acids are overexpressed in lung or colon tumor, or encode a polypeptide that is overexpressed in lung or colon tumors. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 22-26 and 35 can be found at page 108, lines 21-25, and Table 7 (Table 8 as amended herein) on page 114 of the substitute specification.

Claims 22-29, 32-35, and 37-41 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed May 13, 2004. For the reasons set forth below, Applicants respectfully traverse.

Formal Matters:

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

IDS:

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement mailed May 14, 2002. Applicants submit herewith more detailed information regarding the cited sequences. As to the sequence alignments to SEQ ID NOs: 23, 8, 12, and 6 submitted in the Information Disclosure Statement filed April 29, 2003, Applicants state that they are not relevant to the pending claims to nucleic acids related to SEQ ID NOs: 1 and 2.

Priority Determination:

The PTO has stated that no priority exists in provisional application 60/112851 for the results disclosed in Example 16 of the present application. Applicants submit herewith a copy of the relevant portions of PCT/US99/28634 which disclose the results of Example 16. By making this submission, Applicants are not acquiescing to the PTO's determination that the earliest priority date for the present application is the filing of PCT/US99/28634 on December 1, 1999. Applicants reserve the right to argue that they are entitled to an earlier priority date based on the disclosure of SEQ ID NOs: 1 and 2 in U.S. provisional application 60/112851, filed December 16, 1998.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO has rejected Claims 22-31 and 35-41 under 35 U.S.C. § 112, first paragraph, because in its view, while the specification is enabling for nucleic acids of SEQ ID NO: 1 or fragments of such that are usable as hybridization probes, it is not enabling for degenerate variants of SEQ ID NO: 1, for nucleic acids with 80, 85, 90 or 95% identity to SEQ ID NO: 1, for nucleic acids with 80, 85, 90 or 95% identity to a sequences which encodes a protein of SEQ ID NO: 2, or for nucleic acids which hybridize to any of the above. Applicants respectfully disagree.

Applicants note that the PTO has acknowledged that nucleic acids of SEQ ID NO: 1 and their fragments have utility as probes, because the nucleic acid of SEQ ID NO: 1 is amplified in a certain cancer cells. (Office Action at page 4). Applicants respectfully disagree with the PTO's statement that the use of a nucleic acid as a hybridization probe does not confer utility to the protein encoded by the nucleic acid, or to nucleic acids that vary from the one originally identified. Applicants submit that because the nucleic acid of SEQ ID NO: 1 is overexpressed in certain cancers, the protein that SEQ ID NO: 1 encodes also has utility in diagnosing and typing tissue samples. Thus, nucleic acids which encode the polypeptide of SEQ ID NO: 2 have utility as well and are enabled.

It is well-established in the art that where a nucleic acid is overexpressed, it is more likely than not that the protein encoded by the peptide is also overexpressed. While there are known exceptions to this general rule, the working hypothesis among those skilled in the art is that if a

gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. Thus, as SEQ ID NO: 1 is overexpressed in certain cancer cells, one of skill in the art would also expect that the protein encoded by SEQ ID NO: 1 (that is the polypeptide of SEQ ID NO: 2) is also overexpressed in certain cancer cells. This makes polypeptides of SEQ ID NO: 2 useful as a diagnostic tool. It follows that nucleic acids which encode a polypeptide of SEQ ID NO: 2 are also useful for the production of that polypeptide.

Applicants enclose a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration was submitted in connection with co-pending application Serial No. 10/006,867. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is overexpressed...the gene product or polypeptide will also be overexpressed." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6). Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between an increase in gene expression and the level of the encoded protein.

As recognized by the PTO, the data presented in Table 7 (Table 8 as amended herein) on page 114 of the substitute specification indicate that the gene encoding the PRO1800 polypeptide is amplified in cancerous tissue. The general, accepted understanding in the art is that the level of protein expression would therefore also be increased, and thus the polypeptide would be a

useful diagnostic tool – for example, to generate antibodies to detect the presence of PRO1800 peptide in cancer cells.

Applicants believe they have supplied sufficient evidence to show that there is a significant correlation between gene amplification and protein expression. However, even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer, and corresponding antibodies, would still have utility. Enclosed is a copy of a Declaration by Avi Ashkenazi, an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925.

As explained in paragraph 6 of the Ashkenazi Declaration:

> Even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

This statement is echoed by Mr. Grimaldi in his declaration at paragraph 6.

Therefore, according to Dr. Ashkenazi and Mr. Grimaldi, medical practitioners who are interested in diagnosing cancer would not only want to know whether certain nucleic acids are overexpressed, but also whether the gene products are overexpressed as well. This information determines the course of recommended therapy.

As set forth on page 83, lines 17-20 of the substitute specification, the disclosed proteins of the invention can be used for tissue typing. In addition, as indicated on page 88, lines 3-5 of the substitute specification, the disclosed proteins can be used to generate antibodies to PRO1800 proteins. Table 7 (Table 8 as amended herein) identifies several tissue types, all obtained from cancerous tumors, in which PRO1800 nucleic acids are amplified. As a result, PRO1800 nucleic acids, as well as polypeptides and antibodies, can be used diagnostically in determining whether a particular tissue type obtained from a patient is cancerous or not, and to more accurately determine the type of tumor. Thus, those of skill in the art recognize the utility of the PRO1800

polypeptide as a diagnostic and therapeutic tool. It follows that nucleotide sequences which encode these useful diagnostic tools would also have an enabled use.

Conclusion

Applicants submit that because there is a specific, substantial and credible utility for the PRO1800 polypeptides in diagnosing and typing cancer cells, it follows that polynucleotide sequences encoding those peptides have utility in addition to use as hybridization probes. Thus, polynucleotide sequences which are claimed by what they encode, rather than the structure of the nucleic acid, are enabled. Polynucleotides encoding the polypeptide of SEQ ID NO: 2 have utility in producing polypeptides for use as diagnostic tools.

Applicants have provided several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, and Drs. Polakis, and Ashkenazi, and must treat as true the statements made by these experts. Applicants remind the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001). In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection of Claims 22-29, 35, and 37-41 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. § 112, first paragraph – Written Description

The PTO has rejected Claims 22-27, 30-31, and 35-41 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The PTO argues that there is "no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any specific feature that is disclosed as being associated with PRO1800," and therefore the claims are drawn to a genus of polynucleotides that are defined only by sequence identity. (Office Action at page 6). Applicants respectfully disagree.

Applicants initially note that Claim 27 does not include any percent sequence identity language, and therefore Applicants respectfully submit that rejection based on the argument that the claims are drawn to a large genus defined only by sequence identity clearly do not apply to this claim.

With respect to Claims 22-26, 35, and 37-41, as amended these claims require that the claimed isolated nucleic acids be overexpressed in lung or colon tumor, or encode a polypeptide that is overexpressed in lung or colon tumors. Thus, there is a specific expression pattern as well as disease or condition associated with the claimed nucleic acid sequence. Applicants therefore believe that they have provided sufficient distinguishing characteristics of the genus to satisfy the written description requirement. Applicants respectfully request that the PTO reconsider and withdraw the written description rejection of Claims 22-27, 35 and 37-41 under 35 U.S.C. §112, first paragraph.

Deposit Requirement

The specification has been amended to state that the deposit of biological materials will be maintained for a term of at least 30 years and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository. Therefore, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 22-41 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "the extracellular domain" as no extracellular domain has been described. Applicants have amended the claims to delete any reference to an extracellular domain. The PTO also objects to the use of the phrase "hybridizes to" as indefinite because there is no limiting definition of the phrase in the specification. Finally the PTO objects to the term "stringent conditions" as being indefinite because it is a relative term. Applicants have amended claims 35 and 37 to specify the conditions under which the hybridization occurs. Applicants submit that "hybridizes to" has a well-established meaning in the art and that it is not indefinite, particularly where the specific conditions under which hybridization is assessed have

been specified. Thus, applicants request that the PTO reconsider and withdraw the indefiniteness rejection of Claims 22-29, 32-35, and 37-41 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. § 102(b) – Anticipation

The PTO has rejected Claims 35-37 under 35 U.S.C. § 102(b) as being anticipated by F. Gabrielli et al., Eur. J. Biochem 232:473, 1995 (hereinafter Gabrielli). The PTO asserts that the Gabrielli discloses a protein which is 62% indentical to SEQ ID NO: 2. The PTO asserts that the nucleic acid encoding the protein would have sufficient regions of identity to SEQ ID NO: 1 so as to hybridize to it, even under stringent conditions. Applicants submit that Gabrielli does not anticipate Claim 35 and 37 because it fails to teach each and every element of the claimed invention.

Under 35 U.S.C. §102(b), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). As amended, Claims 35 and 37 require that the isolated nucleic acid be overexpressed in lung or colon tumor, or encode a polypeptide that is overexpressed in lung or colon tumors. This limitation is not disclosed in Gabrielli, and therefore, even if the sequence disclosed in Gabrielli hybridized to SEQ ID NO: 1 under stringent conditions, it does not anticipate Claims 35 or 37. For this reason, applicants request that the PTO reconsider and withdraw the anticipation rejection of Claims 35 and 37 under 35 U.S.C. §102(b) based on Gabrielli.

The PTO has rejected Claims 22-32 and 34-41 under 35 U.S.C. § 102(b) as being anticipated by DE 198 18 620 (Rosenthal et al.) (hereinafter Rosenthal). The PTO asserts that Rosenthal discloses a nucleic acid, SEQ ID NO: 10, which is 100% identical to SEQ ID NO: 1 of the instant application, with the exception of nine nucleotides at the amino terminus of SEQ ID NO: 1. The PTO also asserts that Rosenthal discloses vectors, host cells, and fusion constructs, and that numerous disclosed vectors are specific to *E. coli.* Applicants submit that Rosenthal is not prior art under 35 U.S.C. § 102(b), and does not anticipate Claim 32 because it fails to teach each and every element of the claimed invention.

To anticipate under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Applicants submit that Rosenthal does not anticipate claims

22-29, 32, 34-35, and 37-41 because it was not published more than one year prior to the date of the instant application for patent in the United States. The instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 09/866034 filed May 25,2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US99/28634 filed December 1, 1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/112851 filed December 16, 1998. SEQ ID NOs: 1 and 2 were first disclosed in Figures 1 and 2 of US Provisional Application 60/112851 filed December 16, 1998. Rosenthal was published October 28, 1999. Thus, Rosenthal was not published more than one year prior to the filing of either PCT Application PCT/US99/28634, filed December 1, 1999, or US Provisional Application 60/112851, filed December 16, 1998. The instant application claims priority to both, and therefore Rosenthal cannot be cited as prior art against the instant application under 35 U.S.C. § 102(b).

In addition, under 35 U.S.C. §102(b), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants note that Rosenthal does not disclose the entirety of SEQ ID NO: 1, and thus cannot anticipate Claim 32.

For these reasons, applicants request that the PTO reconsider and withdraw the anticipation rejection of Claims 22-29, 32, 34-35, and 37-41 under 35 U.S.C. §102(b) based on Rosenthal.

The PTO has rejected Claims 22-32 and 34-41 under 35 U.S.C. § 102(b) as being anticipated by Genebank locus AF044127 disclosed May 27, 1999. The PTO asserts that the clone is identical to nucleotides 11-terminus of SEQ ID NO: 1 of the instant application and discloses an expression vector and *E. coli* as a host cell. As with Rosenthal, Applicants submit that Genebank locus AF044127 does not anticipate Claim 32 because it fails to teach each and every element of the claimed invention, and is not a 35 U.S.C. § 102(b) reference because it was not published more than a year before the priority date of the instant application.

As an initial matter, Applicants note that Genebank locus AF044127 is not 100% identical to the entirety of SEQ ID NO: 1, and thus cannot anticipate Claim 32. Additionally, Genebank locus AF044127 was disclosed May 27, 1999. Thus, Genebank locus AF044127 was not published more than one year prior to the filing of either PCT Application PCT/US99/28634,

filed December 1, 1999, or US Provisional Application 60/112851, filed December 16, 1998. The instant application claims priority to both, and therefore Genebank locus AF044127 cannot be cited as prior art against the instant application under 35 U.S.C. § 102(b). For these reasons, applicants request that the PTO reconsider and withdraw the anticipation rejection of Claims 22-29, 32, 34-35, and 37-41 under 35 U.S.C. §102(b) based on Genebank locus AF044127.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance. Nevertheless, the PTO is invited to contact the undersigned at the telephone number appearing below to discuss any remaining issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 9, 2004

By: _____

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